Treatment Considerations for Patients With Neuropathic Pain and Other Medical Comorbidities

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The efficacy of drugs for neuropathic pain has been established in randomized controlled trials that have excluded patients with comorbid conditions and those taking complex medications. However, patients with neuropathic pain frequently present with complex histories, making direct application of this evidence problematic. Treatment of neuropathic pain needs to be individualized according to the cause of the pain, concomitant diseases, medications, and other individual factors. Tricyclic antidepressants (TCAs), gabapentinoids, selective noradrenergic reuptake inhibitors, and topical lidocaine are the first-line choices; if needed, combination therapy may be used. When a new drug is added, screening for potential drug interactions is recommended. The TCAs have anticholinergic adverse effects and may cause orthostatic hypotension. They should be avoided or used cautiously in patients with cardiac conduction disturbances or arrhythmias. Patients who lack cytochrome P450 2D6 isoenzyme activity are prone to adverse effects of TCAs and venlafaxine and have a weaker analgesic response to tramadol. A combination of several serotoninergic drugs may lead to serotonin syndrome. Risk of gastrointestinal tract bleeding is increased in patients taking selective serotonin reuptake inhibitors or venlafaxine, especially when combined with nonsteroidal anti-inflammatory drugs. Dose adjustment may be needed in patients with renal or hepatic impairment. Depending on the drug, the dose is reduced or the dosage interval lengthened. Slow titration and careful follow-up are needed. No drug is absolutely safe during pregnancy and lactation. Particular care must be exercised during the first trimester when drug dose should be as low as possible. Individual weighing of benefits and risks should guide therapeutic decisions.

***Mayo Clin Proc.* 2010;85(3)(suppl):S15-S25**

ADR = adverse drug reaction; BP = blood pressure; CKD = chronic kidney disease; CYP = cytochrome P450; ECG = electrocardiogram; EM = extensive metabolizer; GFR = glomerular filtration rate; MI = myocardial infarction; NP = neuropathic pain; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio; PM = poor metabolizer; RCT = randomized controlled trial; SNRI = selective noradrenergic reuptake inhibitor; TCA = tricyclic antidepressant; UM = ultrarapid metabolizer

Neuropathic pain (NP), defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system,"[1] is common. In population-based studies, the prevalence of pain with neuropathic characteristics is 7% to 8%,[2,3] including mild cases with no need for symptomatic treatment. The most common reasons for NP are radiculopathies,[4] diabetic polyneuropathy,[5,6] and nerve trauma, including postsurgical neuralgia.[7] Herpes zoster, degeneration of the spine, and stroke are common in elderly patients and cause chronic NP in a substantial number of people. Severe NP causes profound pain, impairs function, and decreases quality of life.[8] Optimized medication can relieve NP and its consequences, such as impaired sleep and depressed mood.[9] Management of NP includes treatment of the causative disease, patient support and counseling, symptomatic pharmacotherapy, and, in the most refractory cases, invasive treatment such as spinal cord stimulation.[10]

Many patients with NP have other chronic disease states that are treated with one or more medications. Multiple medications are often needed to adequately treat chronic diseases, such as hypertension, coronary heart disease, or diabetes mellitus. The number of diseases and medications increases with age, which provides the potential for drug interaction and a consequential increase in adverse events that can substantially affect the patient's quality of life. When pharmacotherapy for NP is planned, the physician should be familiar with the medical history and current medication list of the patient to avoid harmful interactions and to reduce adverse drug reactions (ADRs). The purpose of this article is to review the pharmacology, drug interactions, and drug-disease interactions, particularly cardiovascular considerations, of the drugs used for NP. Further-

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more, use of drugs for NP in patients with renal or hepatic impairment is discussed. The current knowledge of the risks of NP medications during pregnancy and breastfeeding is summarized.

PHARMACOTHERAPY FOR NP

Treatment of NP must be individualized. The etiology of NP, concomitant chronic medical conditions and their medications, individual risks (eg, previous abuse or suicidal history), and costs of treatment need to be considered. In many cases, the adverse-effect profile guides drug selection.

Recent evidence-based guidelines, based on randomized controlled trials (RCTs),[9-13] recommend topical lidocaine, tricyclic antidepressants (TCAs), gabapentinoids (gabapentin and pregabalin), and selective noradrenergic reuptake inhibitors (SNRIs; duloxetine and venlafaxine) as the first-line choices for NP. Carbamazepine and oxcarbazepine are the drugs of choice for trigeminal neuralgia.[11] When the first-line drugs fail to provide acceptable pain relief for NP other than trigeminal neuralgia, tramadol and strong opioids are recommended, as long as the patient has no contraindications for opioid use.[12] Recent observations of opioid-induced endocrine changes and an increase in opioid abuse and diversion have resulted in fewer prescriptions of opioids. Opioids act on the hypothalamic-pituitary-gonadal axis to increase prolactin and decrease gonadotropic hormones, which in turn decrease testosterone levels. This can decrease libido and predispose patients to osteoporosis.[14] Cannabinoids have shown efficacy in treating NP in patients with multiple sclerosis, but because of the potential risks of memory impairment, tolerance, and dependence, cannabinoids are recommended only if multiple sclerosis–related pain is refractory to other medications.[11]

In patients with refractory pain, combination therapy using 2 agents with synergistic mechanisms of action may offer greater pain relief. Although there is compelling animal evidence for combination therapy, few human studies evaluating the efficacy of various drug combinations have been published. In addition, risk of adverse effects and interactions may increase with combination therapies, as reviewed by Virani et al.[15] A combination of gabapentin and an opioid (oxycodone or morphine) achieved better analgesia than either drug alone, but doses may need to be adjusted to improve tolerability.[16-18] Combined gabapentin and nortriptyline therapy is more efficacious than either drug given alone for postherpetic neuralgia.[19]

Some studies have shown negative results of combination therapy. The combination of amitriptyline and fluphenazine was not better than amitriptyline alone for postherpetic neuralgia.[20] In patients with lumbar root pain, morphine, nortriptyline, and their combination failed to provide significant reduction in average leg pain.[21] Mechanisms of action and dosing of the first-line NP drugs and opioids are presented in Table 1. The TCAs, duloxetine, and venlafaxine are not recommended in patients with prostatic hypertrophy and/or urinary retention, whereas they are reasonable for patients with overactive bladder. The TCAs and opioids should be avoided if possible in patients with chronic constipation, or the problem should be treated or attenuated by prescribing the most appropriate drug. Long-term opioid therapy predisposes patients to development of an irregular breathing pattern with central apneas during sleep in a dose-dependent manner and is contraindicated in patients with preexisting central sleep apnea.[22,23] After a treatment trial, the achieved beneficial effects are weighed against ADRs. The most important adverse events and clinical considerations of first-line drugs and opioids are summarized in Table 2.

ADRs ASSOCIATED WITH THE TREATMENT OF NP

Adverse drug reactions are a major public health problem, especially in elderly patients. In western countries, ADRs cause 3% to 6% of all hospital admissions and are responsible for approximately 5% to 10% of inpatient costs.[24] In addition, ADRs may be the fourth to sixth leading cause of death in the United States, and their incidence has remained stable for more than 30 years.[25] Advancing age, comorbidities, number of drugs in use, inappropriate use of medication, alcohol intake, poor cognitive function, and depression are the most important risk factors for the development of ADRs.[24] Drug interactions are an important cause of ADR. Examples of interaction and practical recommendations, based on information in the Swedish-Finnish Interaction X-referencing interaction database,[26] are presented in Table 3. The information in the database is based on published literature and updated regularly according to the latest publications.

A drug-drug interaction can be defined as the effect that one drug has on another drug. Drug-drug interactions can be pharmacokinetic or pharmacodynamic. A pharmacokinetic (what the body does to the drug) interaction involves the effect of one drug on the absorption, distribution, metabolism, or excretion of another drug. Pharmacokinetic interactions can result in changes in serum drug concentrations and might change clinical response. The most frequent pharmacokinetic drug-drug interactions involve several isoenzymes of the hepatic cytochrome P450 (CYP). The isoenzymes CYP2D6 (substrates, eg, amitriptyline, tramadol, and venlafaxine; inhibitors, eg, fluoxetine and duloxetine) and CYP3A4 (substrates, eg, carbamazepine, oxycodone, and venlafaxine; inductors, eg, carbamazepine; inhibitors, eg, grapefruit juice and human immunodeficiency

TABLE 1. **Mechanisms of Action and Dosing of the First-line Drugs and Opioids for Neuropathic Pain**[a]

Medication	Mechanism of action	Starting dose	Titration	Maximum recommended dose
TCAs				
Nortriptyline and desipramine (amitriptyline, imipramine)[b]	Serotonin and noradrenalin reuptake inhibition, sodium channel block, *N*-methyl-D-aspartate receptor antagonist	10-25 mg at bedtime	Increase by 10-25 mg every 3-7 d as tolerated	150 mg/d; further titration guided by blood concentration of the drug and its active metabolite
SNRIs				
Duloxetine	Serotonin and noradrenalin reuptake inhibition	30 mg once daily	Increase to 60 mg once daily after 1 wk	120 mg/d
Venlafaxine	Serotonin and noradrenalin reuptake inhibition	37.5 mg once or twice daily	Increase by 75 mg each week	225 mg/d
Gabapentinoids				
Gabapentin	Calcium channel α_2-δ ligand, which reduces release of presynaptic transmitters	100-300 mg at bedtime	Increase by 100-300 mg 3 times daily every 1-7 d as tolerated	3600 mg/d (divided into 3 doses)
Pregabalin	Calcium channel α_2-δ ligand, which reduces release of presynaptic transmitters	75 mg twice daily	Increase to 300 mg/d after 3-7 d, then by 150 mg/d every 3-7 d as tolerated	600 mg/d (divided into 2-3 doses)
Topical lidocaine				
5% lidocaine patch	Block of peripheral sodium channels and thus of ectopic discharges	Maximum 3 patches daily for a maximum of 12 h	None needed	Maximum 3 patches daily for a maximum of 12 h
Sodium channel blockers[c]				
Carbamazepine	Sodium channel block	100 mg twice daily	Increase by 100 mg twice daily every 3-7 d as tolerated	1200 mg/d; further titration guided by blood concentration of the drug
Oxcarbazepine	Sodium channel block	150 mg twice daily	Increase by 150 mg twice daily every 3-7 d as tolerated	1800 mg/d; further titration guided by blood concentration of the drug
Opioid agonists				
Tramadol	μ-Opioid receptor agonist and serotonin and noradrenalin reuptake inhibition	50 mg once or twice daily	Increase by 50-100 mg/d in divided doses every 3-7 d as tolerated	400 mg/d; in patients >75 y, 300 mg/d
Morphine, oxycodone, methadone, levorphanol, and fentanyl		10-15 mg morphine every 4 h or as needed (equianalgesic dosages should be used for other opioid analgesics)	Increase by 50-100 mg/d in divided doses every 3-7 d as tolerated	Evaluation by pain specialist is highly recommended at relatively high dosages (eg, 120-180 mg/d of morphine; equianalgesic dosages should be used for other opioid analgesics)

[a] SNRI = selective noradrenergic reuptake inhibitor; TCA = tricyclic antidepressant.
[b] Secondary amine TCAs (nortriptyline and desipramine) are preferred because of better tolerability. Use of a tertiary amine TCA (amitriptyline or imipramine) is recommended only if a secondary amine TCA is not available.
[c] Recommended for trigeminal neuralgia.
Adapted from *Pain*,[12] with permission of the International Association for the Study of Pain® (IASP®). This table cannot be reproduced for any other purpose without permission.

virus protease inhibitors) are clinically most important. Gabapentinoids are excreted in urine without metabolism and hence have few pharmacokinetic interactions. However, interactions occur in absorption. For example, coadministration of gabapentin with antacids containing aluminum and magnesium reduced gabapentin bioavailability by up to 24%. In a study with healthy volunteers, gabapentin significantly enhanced the analgesic effect of morphine.[27] It is recommended that gabapentin be taken, at the earliest, 2 hours after antacid administration.

Pharmacodynamics (what the drug does to the body) is related to the pharmacological activity of the interacting drugs. Pharmacodynamic interactions can lead to amplification or reduction in the therapeutic effects or adverse effects of a specific drug.[28] A pharmacodynamic interaction may be due to irrational prescribing, such as initiation of TCA (with anticholinergic effect) in a patient with Alzheimer disease treated with an acetylcholinesterase inhibitor, which may lead to deterioration of the cognitive status. Even with rational polypharmacy, a combination of 2 drugs

TABLE 2. **Adverse Drug Reactions, Precautions, and Contraindications of Drugs Recommended for Neuropathic Pain**[a]

Medication	Major adverse effects	Precautions[b]	Contraindications	Comments, recommendations
TCAs				
Nortriptyline and desipramine (amitriptyline, imipramine)	Cardiac conduction block, sedation, confusion, anticholinergic effects (dry mouth, constipation, urinary retention, blurred vision), orthostatic hypotension, weight gain	Use with caution in patients with history of seizures, prostatic hypertrophy, urinary retention, chronic constipation, narrow-angle glaucoma, increased intraocular pressure, or suicidal ideation; use with caution in patients receiving concomitant SSRI, SNRI, or tramadol treatment	Recovery phase after myocardial infarction, arrhythmias (particularly heart block of any degree), concomitant use of MAO inhibitors, porphyria	ECG screening recommended in adults >40 y; heart rate and blood pressure follow-up (both supine and standing measurements) recommended with dose escalation; ECG and blood concentration follow-up recommended at doses >150 mg/d; follow-up of weight recommended, especially in diabetic patients
SNRIs				
Duloxetine	Nausea, loss of appetite, constipation, sedation, dry mouth, hyperhidrosis, anxiety	Use with caution in patients with history of mania, seizures, or bleeding tendency or those taking anticoagulants; use with caution in patients taking concomitant SSRI or tramadol treatment	Concomitant use of MAO inhibitors; uncontrolled hypertension	Blood pressure follow-up recommended in patients with known hypertension and/or other cardiac disease, especially during the first month of treatment; smokers have almost 50% lower plasma concentrations of duloxetine compared with nonsmokers
Venlafaxine	Nausea, loss of appetite, hypertension, sedation, insomnia, anxiety, dry mouth, hyperhidrosis, constipation	Use with caution in patients with hypertension; use with caution in patients taking concomitant SSRI or tramadol treatment	Concomitant use of MAO inhibitors	Blood pressure follow-up recommended
Gabapentinoids				
Gabapentin	Sedation, dizziness, weight gain, edema, blurred vision	Simple antacids reduce bioavailability		Follow-up of weight recommended, especially in diabetic patients
Pregabalin	Sedation, dizziness, weight gain, edema, blurred vision			Follow-up of weight recommended, especially in diabetic patients
Topical lidocaine				
5% lidocaine patch	Local erythema, rash; no systemic adverse effects		Known history of sensitivity to local anesthetics of the amide type	Systemic absorption <5%
Sodium channel blockers				
Carbamazepine	Somnolence, dizziness, headache, ataxia, nystagmus, diplopia, blurred vision, nausea, rash, hyponatremia, leukopenia, thrombocytopenia, hepatotoxicity	Consider risk of pharmacokinetic interactions with concomitant medications	Atrioventricular block, concomitant use of MAO inhibitors, porphyria	Liver enzymes, blood cells, platelets, and sodium levels should be monitored, at least during the first year; induction of microsomal enzymes may influence metabolism of several drugs
Oxcarbazepine	Somnolence, dizziness, headache, diplopia, nausea, fatigue, hyponatremia, ataxia	25%-30% risk of cross-allergy with carbamazepine		Does not entail enzymatic induction; sodium levels should be controlled during the first months of treatment
Opioid agonists				
Tramadol	Nausea, dizziness, sedation, headache, constipation, dry mouth, hyperhidrosis, seizures, orthostatic hypotension	Risk of dependence and abuse; potential to cause withdrawal with abrupt discontinuation; use with caution in patients with history of seizures; use with caution in patients taking concomitant SSRI or SNRI treatment	Concomitant use of MAO inhibitors	Potential to cause withdrawal with abrupt discontinuation
Morphine, oxycodone, methadone, levorphanol, and pethidine	Somnolence, nausea, constipation, itch, hyperhidrosis, dry mouth, myoclonus, respiratory depression	Risk of dependence and abuse; potential to cause withdrawal with abrupt discontinuation; use with caution in patients with history of seizures or impaired respiratory function	Respiratory depression; concomitant use of MAO inhibitors	"Opioid agreement" recommended; coadministration of preemptive stool softeners recommended; pretreatment ECG screening and follow-up recommended for methadone; pethidine is contraindicated because of the potential for pethidine toxicity with long-term dosing, particularly in patients with renal impairment

[a] ECG = electrocardiography; MAO = monoamine oxidase; SNRI = selective noradrenergic reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

[b] Precautions in patients with renal or hepatic impairment are presented in Table 5.

TABLE 3. **Examples of Interactions and Practical Recommendations of Drugs Recommended for Neuropathic Pain**

	Ibuprofen (NSAID)	Tramadol (prodrug, activated by CYP2D6)	Paroxetine (SSRI, strong CYP2D6 inhibitor)	Carbamazepine (CYP3A4 substrate and inducer)	Warfarin
Amitriptyline, nortriptyline, and desipramine	Concomitant use may increase risk of upper GI tract bleeding; in long-term concomitant use, monitor blood cell counts and consider use of gastroprotection (eg, proton pump inhibitors) (B4)	Concomitant use of tramadol and other serotonergics may cause serotonin syndrome; choose an alternative analgesic that does not increase serotonin activity (C1)	Increased plasma levels and toxicity of amitriptyline; additive effects on monoamines; if concomitant use is considered necessary, monitor plasma concentrations of TCA and consider dose reduction; consider use of an SSRI that does not inhibit CYP2D6 (eg, citalopram) (C3)	Carbamazepine may reduce the serum levels of TCAs; impaired therapeutic response to TCAs may occur; monitor therapeutic response and serum levels of TCAs when concurrent carbamazepine is used; consider use of oxcarbazepine instead of carbamazepine (C4)	Concomitant use may be associated with increased risk of bleeding; careful monitoring of signs and symptoms of acute and/or chronic bleeding is recommended in concomitant use (B0)
Venlafaxine	Concomitant use of NSAIDs and SSRIs or venlafaxine significantly increases risk of GI bleeding; if concomitant use cannot be avoided, consider use of gastroprotection with a proton pump inhibitor (C4)	Concomitant use of tramadol and other serotonergic drugs may cause serotonin syndrome; choose an alternative analgesic that does not increase serotonin activity (C1)	Increased frequency of anticholinergic adverse effects and a few cases of serotonin syndrome have been reported in patients treated with both drugs; avoid combination; if a combination of an SSRI and venlafaxine is desired, choose an SSRI without significant effect on CYP2D6 activity (eg, citalopram) (D4)	Venlafaxine exposure may be decreased in some patients; careful monitoring of therapeutic response to venlafaxine is recommended; therapeutic drug monitoring can be used to titrate the venlafaxine dose (B3)	Risk of bleeding may be increased in concomitant use; signs of increased anticoagulant response and bleeding (blood hemoglobin concentration) should be carefully monitored in concomitant use (C0)
Duloxetine	Concomitant use may increase the risk of upper GI tract bleeding; in long-term concomitant use, monitor blood cell counts and consider use of gastroprotection (eg, proton pump inhibitors) (C0)	Concomitant use may decrease the analgesic effect of tramadol; concomitant use of duloxetine and tramadol may predispose patients to serotonin overactivity and serotonin syndrome; avoid combination; choose an analgesic other than tramadol (D0)	Concomitant use of paroxetine and duloxetine increases the plasma concentrations of both drugs and the risk of serotonergic and possibly anticholinergic adverse effects; avoid combination (D3)	Duloxetine exposure may be decreased in concomitant use; monitor therapeutic effect of duloxetine in concomitant use; duloxetine dose may need to be increased (B0)	Duloxetine may impair thrombocyte function and thus increase risk of bleeding; 1 case report of increased INR from concomitant treatment; signs of increased anticoagulant response (INR) and bleeding (blood hemoglobin concentration) should be monitored in concomitant use (C2)
Carbamazepine	No interactions were found with the given substances	Carbamazepine may reduce and shorten analgesic effect of tramadol; concurrent tramadol may lower seizure threshold; combination should be avoided when possible; analgesic response to tramadol should be carefully monitored in concurrent use (C3)	No interactions were found with the given substances	Not applicable	Carbamazepine reduces anticoagulative response to warfarin if used concomitantly; overanticoagulation may occur in patients stabilized with warfarin and carbamazepine when carbamazepine use is stopped without readjustment of warfarin doses; frequent monitoring of INR is recommended when carbamazepine is added to or withdrawn from regimen of patient taking warfarin; dose reduction of about 50% may be needed on discontinuation of carbamazepine; oxcarbazepine may be used instead of carbamazepine (C4)
Oxycodone	No interactions were found with the given substances	No interactions were found with the given substances	Concurrent use may change the formation of oxycodone metabolites; clinical relevance of this interaction unknown (B0)	Oxycodone blood concentrations may decrease significantly; therapeutic response to oxycodone may be abolished; concurrent use of oxycodone with antiepileptics that strongly induce CYP3A4 should be avoided (C0)	No interactions were found with the given substances

Classification: A, minor interaction of no clinical relevance; B, clinical outcome of the interaction is uncertain and/or may vary; C, clinically relevant interaction that can be handled by dose adjustments, for example; and D, clinically relevant interaction that is best avoided. **Level of documentation**: 0, data derived from extrapolation on the basis of studies with similar drugs; 1, data derived from incomplete case reports and/or in vitro studies; 3, data derived from studies among healthy volunteers and/or on pilot studies among patients; and 4, data derived from controlled studies in relevant patient population. CYP = cytochrome P450; GI = gastrointestinal; INR = international normalized ratio; NSAID = nonsteroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.
Data from the Swedish-Finnish Interaction X-referencing interaction database.[26]

with central nervous system actions and pharmacodynamic interactions may cause dizziness, tiredness, and even confusion unless slowly titrated and carefully monitored.

POLYMORPHISMS AND INTERACTIONS IN THE CYP2D6 ISOENZYME

Most antidepressants are metabolized by the CYP2D6 isoenzyme. The *CYP2D6* gene is highly polymorphic. Individuals with 2 nonfunctional alleles are classified as poor metabolizers (PMs), individuals with one functional allele as intermediate metabolizers, and individuals with 2 functional alleleles as extensive metabolizers (EMs). Ultrarapid metabolizers (UMs) have more than 2 functional copies of the *CYP2D6* gene and exhibit extremely high enzymatic activity.[29] Both genetic polymorphisms and coadministration of CYP2D6 inhibitors modify the clinical effect of the CYP2D6 substrates. Tramadol exerts its analgesic action by increasing noradrenergic and serotonergic neurotransmission in the central nervous system. Tramadol is also a prodrug that is demethylated to an active metabolite, trans-O-desmethyltramadol, by the CYP2D6 isoenzyme. This biotransformation is a prerequisite for the clinical opioid effect of tramadol. The PMs lack this bioactivation and have a weaker analgesic response to tramadol compared with the EMs and UMs. A potent CYP2D6 inhibitor (eg, paroxetine) inhibits biotransformation of tramadol to its opioid agonist metabolite and hence weakens the pain-relieving effect of tramadol in EMs and PMs. The UMs are more sensitive to tramadol and may experience opioid-related adverse events.[30] Life-threatening opioid intoxication has been reported in association with codeine use in a UM.[31]

The TCAs are metabolized by the CYP2D6 isoenzyme. They have a relatively narrow therapeutic range. The PMs achieve therapeutic serum concentrations with lower doses because of the absence of CYP2D6-mediated metabolism and are prone to cardiotoxicity with high doses, whereas the UMs may need high doses to achieve a therapeutic effect. In the EMs and UMs, concomitant use of a potent CYP2D6 inhibitor decreases metabolism of TCAs and increases plasma levels. Additionally, the PMs are prone to adverse effects of venlafaxine.[32] *CYP2D6* genotyping is used in oncology[33] and psychiatry but rarely in pain treatment. In pain treatment, titration of TCAs can be facilitated by blood concentration when a high dose is needed for therapeutic effect or when adverse effects occur with a low dose.

SEROTONIN SYNDROME

A well-established pharmacodynamic drug-drug interaction in the management of NP is serotonin syndrome (ie, excessive serotoninergic agonism due to concomitant use of several serotoninergic drugs, eg, TCAs, SNRIs, tramadol, weight-reducing agents, and triptans).[34] Symptoms include mental status changes, autonomic hyperactivity, and neuromuscular abnormalities. Clinical presentation varies from barely perceptible to lethal, with the latter usually associated with intentional intoxication. Typical first symptoms are agitation, tremor, tachycardia, hypertension, diarrhea, and sweating. One problem is that these symptoms may not be associated with a drug interaction. Mild cases of serotonin syndrome resolve within 24 hours after discontinuation of serotoninergic drug therapy.

RISK OF GASTROINTESTINAL BLEEDING IN THE TREATMENT OF NP

Many patients with NP have concomitant musculoskeletal pain and may use nonsteroidal anti-inflammatory drugs (NSAIDs) on a regular basis. These drugs interfere with the blood coagulation system by inhibiting the synthesis of prostaglandins, which are involved in thrombocyte aggregation. Furthermore, NSAIDs damage the gastrointestinal mucosa. Antidepressant drugs that inhibit serotonin reuptake may also impair platelet aggregation by reducing serotonin concentration in platelets. Antidepressants with a relevant blocking action on serotonin reuptake increase the risk of upper gastrointestinal tract bleeding. The increased risk may be of particular relevance when these drugs are taken with NSAIDs.[26] In a recent population-based study, risk of gastrointestinal bleeding was increased in patients using selective serotonin reuptake inhibitors or venlafaxine (odds ratio [OR], 1.6 and 2.9, respectively). An interaction with NSAIDs (OR, 4.8) was observed, in particular among those not taking acid-suppressing agents (OR, 9.1).[35] Hence, long-term use of an NSAID is not recommended with selective serotonin reuptake inhibitors, SNRIs, or TCAs. If long-term use cannot be avoided, a proton pump inhibitor is recommended.[26]

Use of warfarin is common to prevent thrombosis and emboli. Several case reports describe increased prothrombin times and/or bleeding in patients taking the combination of warfarin and tramadol. In a population-based study, the relative risk of major gastrointestinal bleeding was 3.3 with a tramadol-warfarin combination compared with warfarin only.[36] The mechanism of this interaction is not fully understood. However, the combination of tramadol and warfarin should be avoided.[26]

REDUCING THE RISK OF DRUG-DRUG INTERACTIONS

In everyday practice, unnecessary polypharmacy should be avoided, and the medication list should be reviewed regular-

ly. Adding a new drug provides the possibility of discontinuing the use of another drug, and screening for potential drug interactions should be performed. This is best done by using drug interaction software, which can alert the prescriber to potential difficulties. After commencing therapy with a new drug, individual dose escalation of the new agent, possible reoptimization of other medications, patient education, and careful follow-up are needed. New drugs should be tested one by one. In long-term use, the lowest effective dose of each drug should be used.

CARDIOVASCULAR CONSIDERATIONS OF PHARMACOTHERAPY FOR NP

Cardiovascular diseases, such as hypertension, coronary heart disease, and arrhythmia, are common. When a drug for NP is considered, cardiovascular risks of the compound need to be considered. The TCAs have well-characterized cardiovascular effects: orthostatic hypotension, slowed cardiac conduction, type 1A antiarrhythmic activity, and increased heart rate.[37] Orthostatic hypotension is of particular concern in elderly patients and may result in falls and hip fractures, as noted in population-based studies.[38,39] The risk of falls is increased during the first few weeks of treatment.[39] If treatment with a TCA is initiated, selection of a less anticholinergic TCA, low initial dose, slow titration, and follow-up of blood pressure (BP) (measured both when supine and standing) is recommended, especially for elderly patients. The TCAs prolong both PR and QTc intervals. They should be avoided or used with considerable caution in patients with cardiac conduction disturbances or arrhythmias. In psychiatric patients, therapeutic doses of TCAs lengthen the QTc interval independently of the presence of cardiovascular disease, but the clinical importance of this observation is unknown.[40] To minimize the risk of arrhythmia, electrocardiogram (ECG) screening is recommended before treatment with TCAs is initiated in patients older than 40 years.[12] On the basis of observations in the late 1980s, mortality after myocardial infarction (MI) is increased with use of type 1A antiarrhythmic agents. Thus, TCAs are contraindicated after a recent MI. The risk of a sudden cardiac event in patients with a history of coronary heart disease is not fully clarified. An increased risk of MI with TCAs compared with selective serotonin reuptake inhibitors has been reported,[41] but subsequent studies did not confirm this finding.[42,43] A retrospective cohort study showed that TCAs in dosages of less than 100 mg/d did not increase the risk of sudden cardiac death, whereas higher doses of TCAs were associated with a 2- to 3-times increased relative risk.[44] According to RCTs, the average effective dosage of amitriptyline in the treatment of NP is 75 mg/d.[11]

Venlafaxine causes a dose-related increase in BP, particularly in patients receiving daily dosages of greater than 200 mg. Before initiation of venlafaxine therapy, preexisting hypertension should be controlled, and BP should be measured repeatedly during treatment. Venlafaxine should not be used in patients with an identified high risk of a serious cardiac ventricular arrhythmia (eg, those with severe left ventricular dysfunction) or uncontrolled hypertension. Cardiovascular changes may be more common in elderly patients. In a prospective cohort study of elderly patients, 24% of initially normotensive participants and 54% of those with preexisting hypertension experienced an increase in BP, and orthostatic hypotension developed in 29% of the patients. A significant increase in the QTc interval was also found in some patients.[45]

Duloxetine is associated with an increase in BP and clinically important hypertension in some patients. This may be due to the noradrenergic effect of duloxetine. Cases of hypertensive crisis have been reported with duloxetine therapy, especially in patients with preexisting hypertension. Therefore, in patients with known hypertension and/or other cardiac disease, BP monitoring is recommended, especially during the first month of treatment. Duloxetine should be used with caution in patients whose condition could be compromised by an increased heart rate or by an increase in BP.

Postmarketing reports have described congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly patients with cardiovascular compromise during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin therapy may resolve the reaction.[46] In addition, use of pregabalin with angiotensin-converting enzyme inhibitors may increase the risk of developing angioedema of the face, mouth (lips, tongue, gums), throat, and larynx.[47]

Opioids have histamine-releasing and anticholinergic properties that may produce adverse cardiovascular effects, such as hypotension or hypertension, palpitations, and sinus bradycardia. Opioids may cause peripheral vasodilation, which may result in orthostatic hypotension. Methadone may prolong the QTc interval and result in torsades de pointes. The risk of arrhythmia often results from multiple factors, including hypokalemia, structural heart disease, and genetic predisposition. An expert panel recommends ECG screening to measure the QTc interval before initiation of methadone treatment and a follow-up ECG within 30 days and annually. Additional ECG screening is recommended if the daily methadone dosage exceeds 100 mg or if patients have unexplained syncope or seizure. Physicians should also be aware of interactions between methadone and other drugs that possess QT

TABLE 4. **Classification of Chronic Kidney Disease**

Stage	Glomerular filtration rate (mL/min per 1.73 m^2)	Description
1	≥90	Kidney damage with normal or increased glomerular filtration rate, with other evidence (albuminuria, proteinuria, or hematuria) of kidney damage
2	60-89	Mild decrease in glomerular filtration rate
3	30-59	Moderate decrease in glomerular filtration rate
4	15-29	Severe decrease in glomerular filtration rate, before end-stage renal disease
5	<15	Established renal failure, end-stage renal disease

From *Kidney Int*,[49] with permission.

interval–prolonging properties or slow the elimination of methadone.[48]

PHARMACOTHERAPY FOR NP IN PATIENTS WITH RENAL IMPAIRMENT

Chronic kidney disease (CKD) is a worldwide public health problem with increasing incidence and prevalence. The most common causes of CKD are diabetes, high BP, autoimmune diseases, and infections. Chronic kidney disease is defined as kidney damage or a glomerular filtration rate (GFR) of less than 60 mL/min per 1.73 m^2 for 3 months or more.[49] Its prevalence in the US population is 13%.[50] Severity of CKD is classified into 5 stages according to the level of GFR[49] (Table 4). The GFR can be estimated from calibrated serum creatinine and estimating equations. To facilitate detection of CKD, guidelines recommend that clinical laboratories compute and report estimated GFR using estimating equations. If a laboratory does not report estimated GFR, calculators are available on the Web. Physicians have traditionally relied on serum creatinine measurement to assess renal function, but this approach may not accurately reflect the kidney function of an individual because its level also depends on muscle mass. In particular, elderly women may have serious impairment of renal function despite a normal or near-normal serum creatinine level.[51] Nevertheless, the accuracy of these estimating equations is not absolute, and regular follow-up is essential.

Furthermore, CKD affects renal drug elimination by changing glomerular blood flow and filtration, tubular secretion and reabsorption, and renal bioactivation and metabolism. In addition, other pharmacokinetic processes involved in drug disposition (eg, absorption, drug distribution, and metabolism) may be affected. Dosages of drugs cleared renally should be adjusted according to creatinine clearance. Loading doses usually do not need to be adjusted, but maintenance dose adjustment is necessary by reducing the dose, lengthening the dosing interval, or both, depending on the drug. Dose reduction is recommended for drugs with a narrow therapeutic range. Lengthening the dosing interval is recommended when the half-life is longer compared with normal conditions. This strategy has been associated with a lower risk of toxic effects but a higher risk of subtherapeutic drug concentrations, especially toward the end of the dosing interval. Of note, the complicated dosage regimens have a lower adherence rate with a consequential lack of efficacy. Therefore, a balance between changing the dose and adjusting the dosing interval to provide a sensible dosage regimen may provide the best outcomes. Serum drug concentrations should be used to monitor effectiveness and toxicity when appropriate. If a drug is removed from plasma by hemodialysis (eg, gabapentinoids), an additional dose is needed.[52] Dosing of the most important drugs for NP in renal impairment is summarized in Table 5.

PHARMACOTHERAPY FOR NP IN PATIENTS WITH HEPATIC IMPAIRMENT

The liver plays a central role in the pharmacokinetics of most drugs. Liver disease without cirrhosis usually results in mild alterations in drug pharmacokinetics, whereas more profound changes are seen in cirrhosis. Liver dysfunction may reduce the blood or plasma clearance of drugs eliminated by hepatic metabolism or biliary excretion and affect plasma protein binding, which in turn could influence the process of distribution and elimination. Portosystemic shunting, which is common in advanced cirrhosis, may substantially decrease first-pass metabolism. Chronic liver diseases are associated with variable reductions in drug-metabolizing activities. In addition, patients with advanced cirrhosis often have impaired renal function, and dose adjustments may be necessary for drugs eliminated by renal excretion. Moreover, patients with cirrhosis are more sensitive to the adverse effects of drugs that affect the central nervous system (eg, opioids). No simple endogenous marker exists to predict hepatic function with respect to elimination capacity of specific drugs. Drugs must be given with caution to patients with severe hepatic insufficiency, and careful follow-up is mandatory.[53] Examples of dose adjustment in patients with liver impairment are presented in Table 5.

PHARMACOTHERAPY FOR NP DURING PREGNANCY AND BREASTFEEDING

No drug is absolutely safe during pregnancy and lactation. For ethical reasons, RCTs cannot be conducted in pregnant

TABLE 5. **Dosing of Drugs for Neuropathic Pain in Patients With Renal and Hepatic Impairment**

Medication	Biotransformation, elimination	Dosing in renal impairment	Dosing in hepatic impairment
TCAs			
Nortriptyline and amitriptyline	Metabolized by CYP2D6, metabolites excreted in urine	Reduced dose and slow titration recommended; titration guided by blood concentration of the drug and its active metabolite	Pharmacokinetics depends on hepatic blood flow; caution should be exercised when dosing in patients with hepatic impairment
SNRIs			
Duloxetine	Extensively metabolized by CYP1A2 and CYP2D6, followed by conjugation; metabolites are excreted principally in urine	No dosage adjustment needed for patients with creatinine clearance of 30-80 mL/min; contraindicated for patients with creatinine clearance <30 mL/min	Should not be used in patients with liver disease resulting in hepatic impairment
Venlafaxine	Metabolized primarily by CYP2D6 to yield pharmacologically active metabolite and to a lesser extent by CYP3A4	No dosage adjustment needed for patients with glomerular filtration rate >30 mL/min; dose should be reduced by 50% for patients with glomerular filtration rate of 10-30 mL/min, dose given once daily	No dosage adjustment required for patients with mild hepatic impairment; dose should be reduced by 50% for patients with moderate hepatic impairment, dose given once daily
Gabapentinoids			
Gabapentin	Eliminated by renal excretion as unchanged drug	Creatinine clearance ≥80 mL/min: maximum dose, 900-3600 mg/d 50-79 mL/min: maximum dose, 600-1800 mg/d 30-49 mL/min: maximum dose, 300-900 mg/d 15-29 mL/min: maximum dose, 150-600 mg/d <15 mL/min: maximum dose, 150-300 mg/d After hemodialysis, additional dose needed	No dosage adjustment required for patients with hepatic impairment
Pregabalin	Eliminated by renal excretion as unchanged drug	Creatinine clearance ≥60 mL/min: start with 150 mg, maximum dose, 600 mg/d 30-60 mL/min: start with 75 mg, maximum dose, 300 mg/d 15-29 mL/min: start with 25 mg, maximum dose, 150 mg/d <15 mL/min: start with 25 mg, maximum dose, 75 mg/d After hemodialysis, additional dose needed	No dosage adjustment required for patients with hepatic impairment
Topical lidocaine			
5% lidocaine patch			Use of lidocaine patch should be avoided in patients with severe hepatic dysfunction, in whom excessive blood concentrations are theoretically possible
Sodium channel blockers			
Carbamazepine	Metabolized mainly by CYP3A4; metabolites excreted in urine and feces	Reduced dose needed in patients with moderate or severe renal impairment	Contraindicated in patients with hepatic impairment
Oxcarbazepine	Rapidly reduced by cystolic enzymes in liver to its active metabolite, which is metabolized further by conjugation; metabolites predominantly excreted by kidneys	In patients with creatinine clearance <30 mL/min, initiate at half the usual starting dose (300 mg/d) and increase, in at least weekly intervals, to achieve desired clinical response	No dosage adjustment required for patients with mild to moderate hepatic impairment; caution should be exercised when dosing in patients with severe hepatic impairment
Opioid agonists			
Tramadol	Metabolized by CYP2D6 to an opioid agonist metabolite (M)1	For patients with creatinine clearance <30 mL/min, increase dosage interval to 12 h; tramadol is not recommended for patients with severe renal impairment (creatinine clearance <10 mL/min)	Elimination of tramadol may be prolonged; usual initial dosage should be used, but in patients with severe hepatic impairment, dosage interval should be increased to 12 h
Oxycodone	Metabolized by CYP2D6 and CYP3A4	Reduced dose is recommended for patients with creatinine clearance <60 mL/min	Reduced dose recommended for patients with hepatic impairment

CYP = cytochrome P450; SNRI = selective noradrenergic reuptake inhibitor; TCA = tricyclic antidepressant.

or lactating women, and the current methods to assess teratogenity consist mainly of pregnancy registries and case-control surveillance studies. However, this does not adequately determine drug safety.[54] When pharmacotherapy is being considered during pregnancy and lactation, the crucial question is, Does the benefit of the drug outweigh its risks?[55] Experience with the use of drugs for NP during pregnancy is derived mainly from patients with epilepsy and severe depression. These conditions may be detrimental and even life-threatening if untreated during pregnancy, which is not the case with NP. The first trimester (the period of organogenesis with a risk of malformations) should be the period with a minimal drug load. If medication is needed, older drugs with more experience are preferred and should be used at the minimum effective dose for the shortest possible time. During the second and third trimesters (the period of growth and maturation), adverse effects on the central nervous system and endocrine system may occur. On the basis of data from 3 prospective and 10 retrospective studies (with <700 cases total), no increased risk of birth defects was observed with TCAs.[56] Two studies of venlafaxine (with 732 and 150 patients) observed no increased risk of birth defects.[57,58] If medication is needed during pregnancy, preconception planning is ideal. Folic acid supplementation is recommended before conception and during pregnancy for mothers using certain antiepileptics (eg, carbamazepine) to decrease the risk of neural tube defects.[55] The lidocaine patch has not been studied in pregnancy; however, because its effect is local, systemic effects are presumed to be minimal. Nevertheless, this product should be used during pregnancy only if needed. If a central nervous system–acting drug is used during pregnancy, careful follow-up during pregnancy and after childbirth is required. Withdrawal symptoms in the neonate have been reported with TCAs, venlafaxine, and opioids. Detailed information on individual drugs during pregnancy is available from teratology information services.

The passage of a drug into breast milk is influenced by many factors, including its volume of distribution, molecular weight, lipid and water solubility, relative affinity for plasma and milk proteins, the pH of blood and milk, and blood flow to the breast. Lower molecular weight and lipid solubility facilitate the passage of a drug to milk. The ability of the neonate to metabolize and excrete drugs is compromised because of the immature nature of these drug-eliminating systems. Hence, it is prudent to monitor breastfed infants for signs of related adverse effects if the mother is taking medications. In practice, TCAs appear to be relatively safe during breastfeeding, and infant levels of venlafaxine have been documented at well below the 10% level that would prompt concern. Carbamazepine attains significant levels in breast milk, but few adverse effect have been reported. Gabapentin crosses into breast milk at levels approaching 100% of maternal level and is therefore not recommended during breastfeeding.[59] Individual risk-benefit weighing and counseling are needed when medication for NP is being considered during lactation.

CONCLUSION

High-quality evidence usually provided from RCTs is lacking regarding the treatment of patients with NP who have multiple comorbid disease states or impaired renal or hepatic function. Our knowledge of the effect of NP medications during pregnancy and breastfeeding is scant. Clinical judgment, assessment of the risks and benefits for the individual patient, and careful follow-up are needed. Neuropathic pain can have devastating effects on quality of life and psychosocial functioning of affected patients, and treatment should be aimed at relieving this pain with minimal risk. Additional studies are needed on the treatment of NP in these special patient groups.

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